

Review

Surface chemistry of hydroxyapatite for sustainable *n*-butanol production from bio-ethanol

Daniyal Kiani^{1,*} and Jonas Baltrusaitis^{1,*}

SUMMARY

Calcium hydroxyapatite (HAp) has emerged as a green, bifunctional catalyst for the heterogeneous coupling of various biomass-derived molecules, including ethanol to *n*-butanol via the Guerbet reaction. This review critically analyzes the surface chemistry of HAp catalysts based on the available temporally- and spatially-resolved *in situ* and *operando* spectroscopic studies. Specifically, the nature of the isolated acidic and basic surface sites, as well as the acid-base pairs, is elucidated based on chemical probe spectroscopy results. Surface structure-reactivity relationships are also rationalized based on the nature and identity of the surface sites involved in various steps of the Guerbet reaction to produce *n*-butanol over the HAp catalysts. Finally, future directions in experimental investigations are suggested to guide the rational design of improved HAp-based catalysts for the Guerbet reaction and other similar chemistries.

INTRODUCTION

Despite significant advancements in converting biomass-derived hydrocarbon and oxygenate feedstock, their commercial adoption has been slow because of both economic and technological barriers.¹ Utilizing a diverse range of renewable feedstock comes with significant advantages, including the ability to respond to market demand fluctuations and maximize profits of the plant over the lifetime.¹ While government incentives have stimulated the use of bio-feedstock, significant advancements in catalyst design, process development, and intensification are still necessary to expand and integrate these bio-feedstocks to synthesize high-value fuels and chemicals. One of the most important and widely produced bio-feedstock molecules is bio-ethanol. Bio-ethanol production capacity was over 27 billion gallons/year worldwide in 2016, of which the US produced over 15 billion gallons.¹ Its primary use is in blending with gasoline, accounting for 90% of bio-ethanol demand.¹ Bio-ethanol can be obtained from biomass resources by fermentation of a range of raw materials, such as corn, sugarcane, and lignocellulose.² Provided the limit on the maximum ethanol blend level in gasoline and the increase in bio-ethanol production capacity, there is an opportunity to utilize renewable bio-ethanol as a platform chemical to catalytically convert it to value-added fuels and chemicals, such as butanol (C₄H₉OH). Unlike ethanol (C₂H₅OH), C₄H₉OH can be used not only as a fuel additive but also as a fuel directly, given its higher volumetric energy content (26.7 MJ/L), and low heating value basis.^{3,4} Other advantages offered by *n*-C₄H₉OH over C₂H₅OH include that it is immiscible in water and has a lower Reid vapor pressure (i.e., lower volatility and evaporative emissions), making it safer and more economical to process/handle.^{4,5} Moreover, C₄H₉OH has been reported to lower SO_x and NO_x engine emissions in mixtures when compared with gasoline.⁵

The bigger picture

Catalytic conversion of biomass-derived molecules is an essential route for renewable chemical and fuel synthesis as the chemicals industry transitions from fossil fuel-derived hydrocarbons toward more sustainable feedstocks. Understanding the catalyst surface chemistry is of paramount importance for the accelerated development of structure-activity/selectivity relationships that form the basis for the rational design and optimization of catalysts at large. Here, we highlight the state-of-the-art understanding regarding the surface chemistry of hydroxyapatite (HAp)—a catalyst that enables the production of value-added alcohols from bio-ethanol. Given the current state of understanding and the future roadmap provided in this review, we expect this field to progress into a mature, productive avenue for the rational design and application of HAp-based catalysts for various acid-base-catalyzed chemistries, including the Guerbet reaction of ethanol to *n*-butanol.

The material compatibility problems are also substantially less severe for C_4H_9OH than C_2H_5OH , with little or no reported swelling of elastomers and a lower corrosivity toward ferrous metals.⁵ Finally, under the Renewable Fuel Standard,⁶ C_4H_9OH also meets the renewable fuel 20% greenhouse gas emission reduction threshold, making it an extremely lucrative target molecule.^{4,6}

Hallmarks of an effective *green* catalyst include (1) its synthesis via green chemistry techniques that preclude the use of toxic chemicals and solvents, (2) high selectivity, (3) improvement in the overall reaction atom efficiency, and (4) enabling solvent-free product synthesis.⁷ In addition, the catalyst needs to satisfy the basic requirements of high recyclability, stability, and availability. Hydroxyapatite (HAp) is a material that naturally occurs in igneous rock, animal bones, and teeth. Although in its mineral form it can be easily mistaken with more precious stones, such as beryl, amethyst, or olivine, a drop of lime juice is enough to start dissolving it—the reason for which A.G. Werner named it in 1786 using the Greek word “*απαταο*,” meaning “to deceive” or “to mislead.”⁸ Recently, HAp has also emerged as one of the greenest, bio-compatible catalysts of high industrial value because of its unique bifunctional properties and ion-exchange capabilities. While HAp can be sourced naturally, it is synthesized via a simple co-precipitation method for catalytic applications to ensure control over composition, structure, and purity.

The stoichiometric formula of HAp is $Ca_{10}(PO_4)_6(OH)_2$, where the molar Ca/P ratio is 1.67.⁹ A deviation from this stoichiometry by varying the Ca/P ratio in the range of 1.50–1.80 offers non-stoichiometric HAp, which allows tailoring the surface acid-base chemistry and the resulting catalytic properties.^{9–12} Often, the presence of a mixture of several calcium phosphate phases was reported as one of the possible explanations for varying Ca/P ratios different from 1.67.^{10,13} However, it has been recently demonstrated that is indeed possible to vary the Ca/P ratio in clean, well-crystallized HAp samples in the absence of other calcium phosphate phases by changing synthesis pH conditions.¹⁰ In terms of bulk crystalline structure, HAp crystallizes in either the monoclinic or hexagonal crystal systems. The monoclinic HAp (space group $P2_1/b$)¹⁴ is the most ordered, stoichiometric, and thermodynamically stable form of HAp, which can be obtained only at very high temperatures.¹⁵ Hexagonal HAp, on the other hand, belongs to the $P6_3/m$ space group and may be non-stoichiometric.¹⁶

Over the past two decades, HAp has emerged as a green catalyst for bio-feedstock conversion, as seen from the most used keywords in the bibliometric network analysis in Figure 1. Based on 221 literature reports, the network analysis suggests that HAp is finding increased use as a catalyst for chemistries relevant to bio-feedstock upgradation, especially for C–C bond coupling of alcohols via the Guerbet reaction,^{11,17–25} Michael addition,²⁶ and aldol condensation.^{9,27–29}

While excellent reviews on bio-feedstock relevant chemistries, such as the Guerbet reaction^{17,22} to produce *n*- C_4H_9OH from C_2H_5OH , are available in the literature, few reviews focus on the relevant surface chemistry of the HAp catalysts. Therefore, this review aims to provide a thorough understanding of the HAp surface chemistry and structural dynamics that ultimately make it an effective catalyst for C_2H_5OH coupling, based on state-of-the-art *in situ* and *operando* characterization techniques, including infrared (IR) spectroscopy, chemical probe IR studies, nuclear magnetic resonance (NMR), X-ray photoelectron spectroscopy (XPS), and ion scattering spectroscopy (ISS). This review is dedicated to critically analyzing the most advanced, recent literature pertaining to HAp's surface chemistry toward *n*- C_4H_9OH production

¹Department of Chemical & Biomolecular Engineering, Lehigh University, Bethlehem, PA 18015, USA

*Correspondence: dak517@lehigh.edu (D.K.), job314@lehigh.edu (J.B.)
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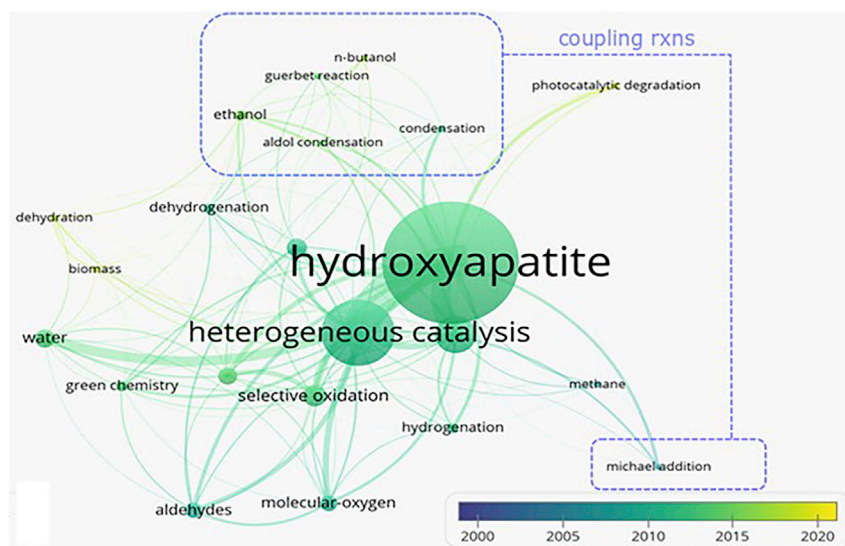


Figure 1. The bibliometric network of "hydroxyapatite catalysis" literature.

This analysis was comprised of 221 reports from the past 2 decades, downloaded from Web of Science in November 2020, generated by VOSviewer. The network was analyzed for keywords occurring at least 5 times. It can be seen that the use of HAp as a heterogeneous catalyst significantly increased around 2010, and typically includes its application in bio-feedstock chemistry, including bond coupling reactions, such as aldol condensation, Michael addition, and the Guerbet reaction. Some literature reports are also present that utilize HAp for hydrocarbon oxidation or dehydrogenation.

from C_2H_5OH to generate structure-performance relationships and highlight avenues for further research. For a broader materials perspective, the reader is directed to existing reviews on HAp synthesis, properties, and applications.^{30,31}

SURFACE STRUCTURE OF HAp

The Ca/P ratio in HAp cannot be set by adjusting the molar concentrations of Ca and P precursors during synthesis only; this is because the Ca/P ratio also depends on how many structural carbonates incorporate into the HAp lattice from ambient CO_2 dissolving into the precursor solution during synthesis.^{10,32–34} Also, the Ca/P ratio in the bulk of the material does not account for the OH^- concentration that is known to be influenced by the presence of structural defects.³² Therefore, a more accurate chemical description for HAp found in the literature is summarized as $Ca_{10-x-B}(PO_4)_6-x-B(HPO_4)_x(CO_3)_{A+B}(OH)_{2-x-2A-B}$, where A and B are related to carbonates located in OH^- and $H_xPO_4^{(3-x)}$ structural sites, respectively.³²

Despite the lack of understanding regarding the effects of bulk composition (i.e., Ca/P ratio, defects, etc.) on the surface composition and structure of HAp, pioneering work in the HAp catalysis literature does provide empirical structure-function relationships in this regard. Specifically, it has been shown that changing the Ca/P bulk ratio during HAp synthesis leads to a systematic change in the kinetics of the various acid- or base-catalyzed steps involved in the reaction mechanism (e.g., in the Guerbet reaction), which was attributed to changes in the density of acidic and basic surface sites with varying the Ca/P ratio.¹¹ However, direct experimental evidence of how the bulk Ca/P ratio effects the surface composition, structure, site density, nature of surface sites, etc., is yet to be revealed. Provided that HAp can contain carbonate, phosphate, and hydroxyl groups, both in the bulk and on the surface, the discrimination between bulk and surface species remains challenging, yet critical, to advancing HAp catalysis. Therefore, the

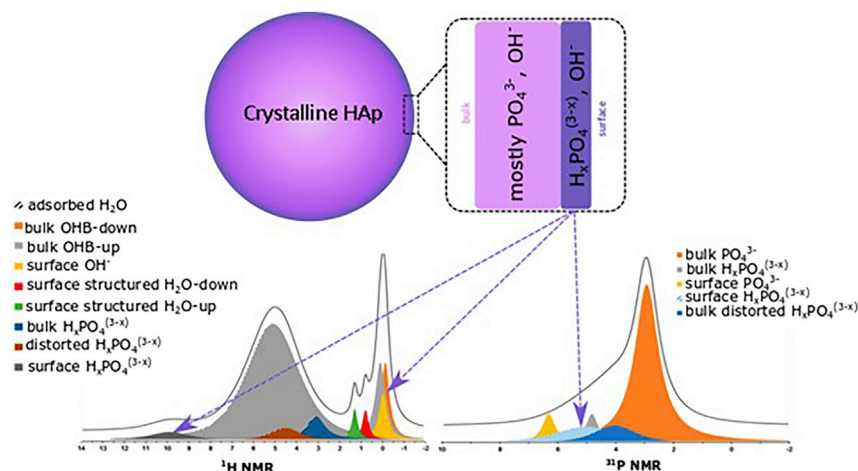


Figure 2. MAS NMR (^1H and ^{31}P) of HAP catalysts.

MAS-NMR results indicate that the HAP surface is comprised of OH^- and $\text{H}_x\text{PO}_4^{(3-x)}$, and PO_4^{3-} sites.

Note that the NMR intensities of the different contributions are not directly representative of their concentration. MAS-NMR adapted from Ben Osman et al.³⁶

following sub-sections attempt to elucidate the HAP surface structure and composition critical to understanding the active surface sites involved in acid-base catalysis, including Guerbet reaction.

Solid-state NMR

NMR-based techniques have widely been utilized to study various structural aspects of HAP. ^{43}Ca solid-state NMR studies have shown that Ca exists as two distinct sites in HAP; Ca(I) and Ca(II), where the Ca(I)/Ca(II) ratio was ~ 0.67 .³⁵ It was hypothesized that Ca(I) could be either 6 or 9 coordinated with an average Ca-O length of 2.43 or 2.55 Å, respectively.³⁵ On the other hand, Ca(II) could be 4, 6, or 7 coordinated, with an average Ca-O length of 2.37, 2.41, or 2.46 Å.³⁵ However, the authors did not attempt to discriminate between bulk versus surface Ca sites. Also note that ^{43}Ca NMR cannot be used to characterize a sample without previous ^{43}Ca enrichment.

While some examples of ^{43}Ca NMR are present in the literature, most literature studies have focused on ^1H and ^{31}P NMR. As summarized in Figure 2, by using 2D solid-state ^1H and ^{31}P MAS-NMR, it was confirmed that the surface of the well-crystallized HAP particles with varying Ca/P ratio pretreated at 623 K under vacuum terminated in mostly protonated-phosphate groups, $\text{H}_x\text{PO}_4^{(3-x)}$ ($x = 0-2$), with a minor population of PO_4^{3-} .³⁶ On the other hand, the bulk structure mostly contained PO_4^{3-} groups in the 3D HAP framework.³⁶ However, defective HPO_4^{2-} species were also identified in the bulk,³⁶ and it was hypothesized that carbonate impurities were responsible for the symmetry perturbation of these protonated-phosphate groups.³⁶ Via controlled synthesis to adjust bulk Ca/P ratios, authors also observed the dependence of relative intensities of the various MAS-NMR contributions corresponding to various bulk and surface hydrogen and phosphorous-containing species on the stoichiometry $\text{Ca}_{10-x}(\text{PO}_4)_6-x(\text{HPO}_4)_x(\text{OH})_{2-x}$. Moreover, a peculiar feature of HAP surface, as it was exposed to ambient conditions, was also observed in the NMR study; the authors not only identified the well-known broad NMR signal associated with water adsorbed on surface Ca^{2+} and $\text{H}_x\text{PO}_4^{(3-x)}$ but also unique signals due to structured water molecule stacking along the vertical axis in continuation with the internal OH^- channels.³⁶ MAS-NMR studies elsewhere in the literature

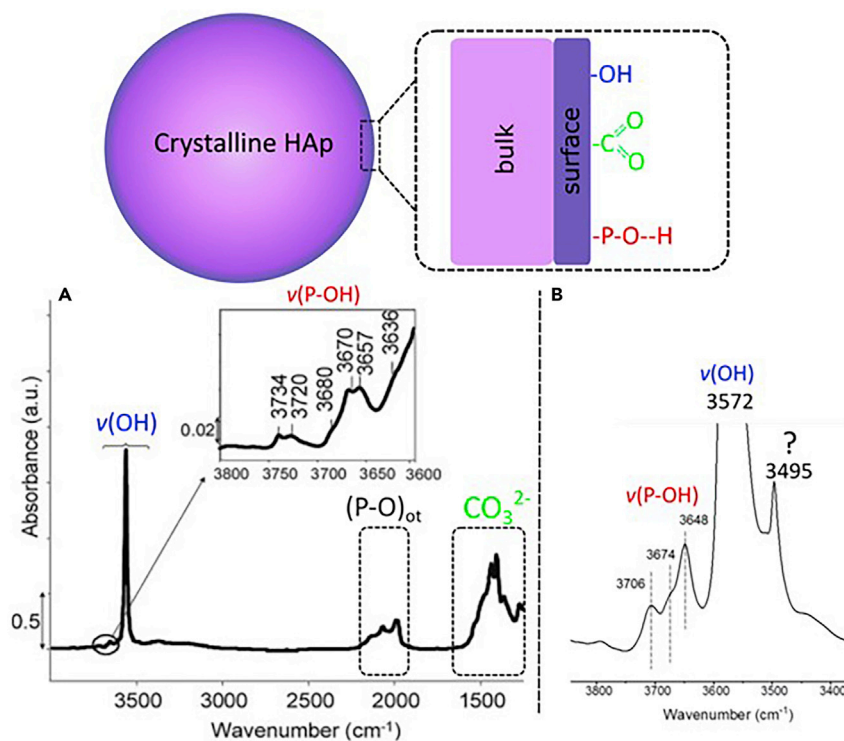


Figure 3. *In situ* IR spectra of HAp catalysts

IR spectra of HAp catalysts exhibit peaks in three main regions: 3,400–4,000 cm⁻¹ region with various peaks from O-H groups, the 1,900–2,100 cm⁻¹ region with P-O overtones, and the 1,300–1,600 cm⁻¹ region with different C-O bands due to carbonates. Figures were adapted from (A) Diallo-Garcia et al.,⁴⁰ copyright American Chemical Society and (B) supplemental information of Wang et al.,¹⁹ copyright John Wiley and Sons.

demonstrated that, even at 800°C, adsorbed water was still present on the HAp surface.³⁷ The unique ability of HAp surface sites to stack water molecules and their propensity to hydrate may be of importance to understanding the surface chemistry of HAp-catalyzed reactions since water is involved in those reactions (*vide infra*).

In situ IR spectroscopy

The structure of HAp has been characterized by vibrational spectroscopies in various modes, including transmission and diffuse reflectance.^{19,38,39} Specifically, *in situ* IR spectroscopy of dehydrated HAp samples exhibited three major IR active regions,^{19,38,39} as summarized in Figure 3A: the 3,400–4,000 cm⁻¹ region with various peaks from O-H groups, the 1,900–2,100 cm⁻¹ region with P-O overtones, and the 1,300–1,600 cm⁻¹ region with different C-O bands due to carbonate impurities. The most informative region from a catalysis perspective to understand the nature of surface functional groups is the 3,400–4,000 cm⁻¹ region. In this IR region, all studies reported a sharp, intense peak at 3,572 cm⁻¹ associated with bulk and surface OH groups.^{19,39} Using C₂H₂ adsorption, and isotope-labeling studies, it was shown that the 3,572 cm⁻¹ peak decreased upon probe molecule adsorption, indicating that there is a contribution from surface OH groups in this peak as well.^{38,40} According to isotopically labeled HAp analysis via IR spectroscopy, the 3,636, 3,670, 3,680, 3,720, and 3,734 cm⁻¹ peaks correspond to the surface P-OH groups, while the 3,657 cm⁻¹ peak belongs to bulk H_xPO₄^{(3-x)-}.⁴⁰ Across various studies, the ratio of surface-to-bulk P-OH vibrations and the exact IR peak positions is expected to vary depending on the sample synthesis procedure, temperature, and the gaseous environment utilized in the study.

Interestingly, a sharp peak at $\sim 3,500\text{ cm}^{-1}$ is also observed in some reports for stoichiometric HAp (Ca/P = 1.67).¹⁹ This sharp peak at $\sim 3,500\text{ cm}^{-1}$ is marked with a “?” in Figure 3B as it has not been assigned, according to the best of our knowledge. Due to the lower wavenumber position of this peak relative to other O-H peaks discussed above, and its narrow shape, it can be hypothesized that this $\sim 3,500\text{ cm}^{-1}$ peak belongs to isolated O-H groups that are acidic (i.e., the O-H bond is weaker than other O-H groups that vibrate at higher wavenumbers), although its exact origin and spatial location, e.g., surface versus bulk, remains unclear. As this peak has largely remained neglected in other IR characterization studies (zoomed-in spectra in this region are not always available), its involvement in the catalytic mechanism over HAp is still not well understood. At a similar position of $\sim 3,534\text{ cm}^{-1}$, a peak was reported in a different study and attributed to O-H groups formed as a result of thermal treatment of the HAp catalyst.³² Moreover, it should be noted that bicarbonates ($\text{H}_x\text{CO}_3^{(2-x)}$) can also exhibit an IR peak at $\sim 3,500\text{ cm}^{-1}$ from C-O-H,⁴¹ and thus the possibility of the IR peak in the $\sim 3,500\text{ cm}^{-1}$ region being the O-H vibration from surface bicarbonate needs to be entertained, and the contribution of such surface $\text{H}_x\text{CO}_3^{(2-x)}$ sites toward HAp-catalyzed reaction investigated.

To the best of our knowledge, *in situ/operando* temperature-programmed desorption (TPD) IR studies (especially in diffused reflectance mode) are not available that could spectro-kinetically elucidate the dynamic evolution of peaks corresponding to various surface OH groups (i.e., P-OH, Ca-OH, C-OH, etc.) as a function of environmental conditions (temperature, gas) and exposure to reaction relevant molecules, such as $\text{C}_2\text{H}_5\text{OH}$, H_2O , etc. Specifically, *in situ* spectroscopic studies can reveal the evolution of surface OH sites from *in situ* hydroxylation/dehydroxylation during $\text{C}_2\text{H}_5\text{OH}$ coupling, where H_2O forms as a by-product. Since the degree of hydroxylation of heterogeneous catalytic materials is a key parameter to tune their reactivity, further temporally resolved *in situ/operando* IR studies are required to fully understand the surface chemistry and reactant-surface interactions of each kind of surface site to ascertain their role toward the reaction.

Surface and sub-surface composition of HAp using XPS and ISS

The surface structure and composition of crystalline materials in general^{42–45} and HAp⁴⁶ in particular are known to differ significantly from the bulk. Preliminary evidence of structural and compositional variation between the surface and sub-surface HAp was obtained using molecular dynamics, which showed that, during thermal treatment, the surface underwent significant restructuring due to OH^- ions migrating outward from the bulk to the surface and bonding with the outer Ca^{2+} ions.^{47,48} The phosphate groups then occupy the holes left by the hydroxyls in the bulk layer. The hydroxyl surface enrichment also leads to a decrease in Ca^{2+} electrophilicity.^{47,48} Moreover, the terminal OH groups from restructuring were suggested to lower the surface energy, making it a thermodynamically favorable process.⁴⁹

Very recently, experimental evidence has emerged that corroborates the Ca enrichment of the surface in HAp.⁴⁶ As depicted in Figure 4, the Ca/P ratio in the amorphous surface layer (top one to three atomic layers; 1 nm) was found to be ~ 7 —much higher than the bulk stoichiometric Ca/P ratio of 1.67.⁴⁶ Semi-quantitative results from ISS also showed that the HAp surface was comprised of 83.5% Ca, 12.5% P, 1.5% O, and 2.5% C (due to carbonate adsorption).⁴⁶ Fundamentally, the reason for this Ca enrichment in HAp and other calcium phosphates is not well understood. It was hypothesized that Ca^{2+} has lower hydration energy than PO_4^{3-} and, in environments where HAp interfaces with water, there may be thermodynamic benefits from having Ca^{2+} occupy sites in the topmost atomic layer of the

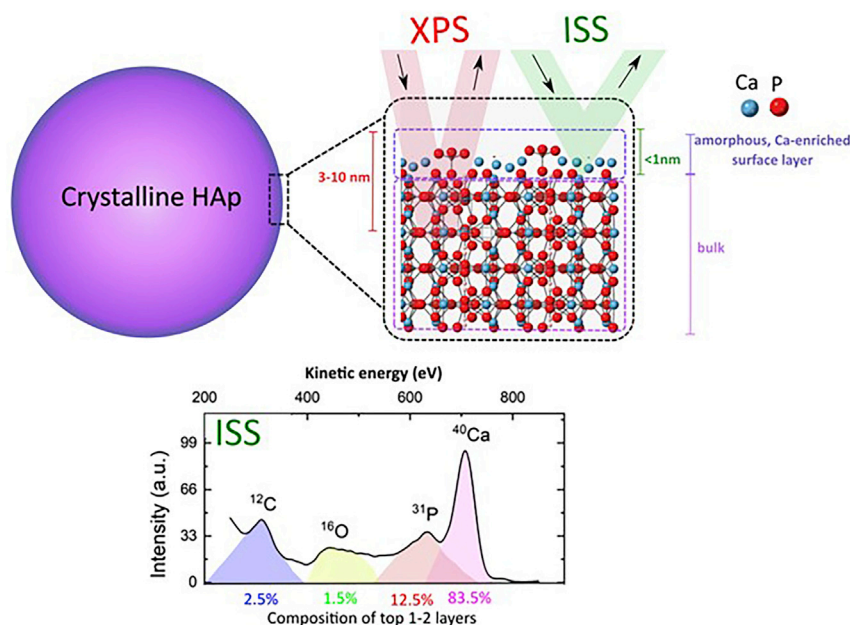


Figure 4. Surface and surface-region composition of HAp via ISS and XPS

Experimental data adapted from Uskokovic⁴⁶ with permission from the PCCP Owner Societies. XPS and ISS probing depths are based on Uskokovic⁴⁶, Venn et al.,⁵¹ Langley,⁵² and Baltrusaitis et al.⁵³

surface.⁴⁶ Also, there may be an enthalpic gain if the surface OH groups and H₂O form short-lived complexes via H bonding.⁴⁶ Another explanation for Ca enrichment of HAp at ambient conditions was postulated using the standard enthalpy of formation for Ca(OH)₂, as opposed to the enthalpy of formation for protonating H_xPO₄^{(3-x)-} (*x* = 0–2) species.⁴⁶ The binding of OH[–] to Ca²⁺ was found to be more favorable than the binding of H⁺ to the H_xPO₄^{3–}.⁴⁶ In agreement, another ISS (also known as low-energy ion scattering [LEIS]) study also found Ca enrichment in the topmost atomic layer in HAp.⁵⁰

The Ca surface enrichment in the top atomic layer in HAp, as demonstrated by the surface-sensitive ISS, is in contrast to XPS studies, which generally point to a Ca-deficient surface, i.e., a Ca/P ratio lower than the bulk ratio across multiple literature studies.^{9,11,39,46,50,54,55} The lower than bulk Ca/P ratio from XPS may be a measurement artifact, as indicated by a steady drop in the Ca/P molar ratio upon prolonged exposure to X-rays (1 h) during XPS analysis, where these ratios ranged from 0.12 to 0.30 lower than the corresponding stoichiometric values depending on the phosphate compound being studied.⁵⁴ It should be noted that parameters used within a study, such as the synthesis method, Ca/P ratio, identity of precursors, atmospheric composition around the synthesis vessel, etc., may also lead to contradictory results between various studies reported in the literature due to the difference in the nature of the synthesized HAp. Other than that, we believe that the compositional difference as observed by XPS (probing depth: 3–10 nm) and ISS (probing depth: top atomic layer) is justified because measurement techniques with different probing depths will give different results regarding the composition.^{46,50} Therefore, a more apt interpretation of XPS results is as being a representative average of both surface and sub-surface i.e. surface region, while ISS results are representative of the true surface as shown in Figure 4. Surprisingly, near ambient pressure (NAP) XPS studies of HAp at/near reaction conditions have not been undertaken to date,

which can provide the most relevant information in contrast to *ex situ* XPS studies conducting measurements at ambient temperature and ultra-high vacuum (UHV) conditions. It is expected that NAP-XPS studies in conjunction with grazing incidence XRD (GIXD; also called surface XRD–SXR) in the future will help resolve the surface composition of HAp catalysts under/near reaction conditions.

NATURE OF HAP SURFACE SITES VIA CHEMICAL PROBE IR STUDIES

The HAp surface is known to contain acid-base pairs.¹⁹ Both Lewis and Brønsted acid-base pairs may be present on the surface and, until very recently, it was not known which of these pairs are active in C₂H₅OH coupling catalysis. Specifically, a Lewis acid-base pair would be constituted of Ca²⁺ and OH[−], while a Brønsted acid-base pair of P–OH and P=O. Alternately, a *mixed* acid-base pair may also be present where a Lewis base (OH[−]) is in the vicinity of a Brønsted acid (P–OH) and vice versa. The sections below are dedicated to the state-of-the-art understanding of isolated acid and base sites as well as the acid-base pairs present on HAp surfaces revealed by chemical probe IR studies.

Carbon monoxide (CO) IR studies

CO is well suited to obtain critical insights on the basicity and acidity of surface HAp sites.²⁹ The Lewis acid on the HAp surface was found to be weak-to-moderate in strength. Using CO adsorption IR spectroscopy, it was shown that, at 303 K, only one IR peak at 2,181 cm^{−1} was present.⁵⁶ The maximum intensity of the band attained under progressively increasing CO pressures was found to be extremely low, leading to the conclusion that HAp surface cations were weak Lewis acidic sites.⁵⁶ Moreover, based on the low value of heat of adsorption calculated as a function of increasing uptake at 303 K for a HAp sample dehydrated at 573 K, it was concluded that only a small fraction (~5%) of the surface Ca²⁺ sites were acidic enough for CO adsorption, suggesting the overall weak Lewis acidity of the HAp surface.⁵⁶ Similar results of CO probing indicating weak, marginally reactive Lewis acid sites on the HAp surface were also reported.^{29,57,58} Interestingly, one study deconvoluted the CO adsorption bands in the 2,100–2,200 cm^{−1} range into the following five bands: ~2,182 cm^{−1} from CO adsorbed on Ca²⁺, and the four contributions at ~2,177, ~2,171, ~2,164, and ~2,152 cm^{−1} from CO interacting with various Brønsted acidic P–OH surface groups. According to this interpretation, the authors concluded that the HAp surface has both weak Lewis acidic Ca²⁺ and Brønsted acidic P–OH sites.³⁹

Pyridine (C₅H₅N) IR spectroscopy

IR peaks at 1,597, 1,574, 1,488, and 1,441 cm^{−1} observed for pyridine (C₅H₅N) chemisorbed on HAp surface were attributed to Lewis acid sites,⁵⁷ while the peaks at 1,604, 1,588, and 1,434 cm^{−1} to physisorbed pyridine.⁵⁷ As the sample was purged with He and the temperature increased, all bands decreased to almost zero by 100°C. These results confirm that pyridine weakly adsorbs on the HAp surface on Lewis acid sites—corroborating the weak strength of Lewis acid sites suggested from CO adsorption studies. Even though the authors concluded that no Brønsted acid peak was observed in 1,540–1,545 cm^{−1}, a small peak (highlighted in red in Figure 5) is in fact present in the spectrum. The presence of Brønsted acidity in HAp is controversial as some reports provide evidence for their presence,⁵⁵ while others do not.²⁹ The disagreement on the presence of Brønsted acid sites on the HAp surface is yet to be resolved and requires careful spectroscopic characterization of model samples prepared via various synthesis methods with different Ca/P ratios under controlled conditions of measurement. Finally, another commonly used basic probe, ammonia (NH₃), could be used to verify the presence of Brønsted acid sites. It

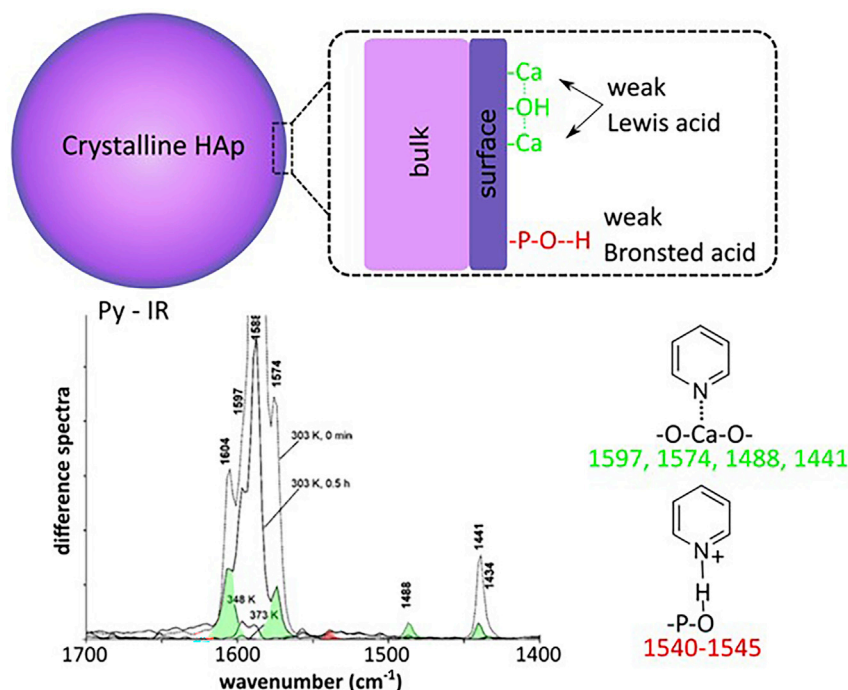


Figure 5. Pyridine adsorption IR spectroscopy of HAp catalysts.

Weak IR peaks due to pyridine adsorption on Lewis and Brønsted acid sites were observed. . . Data adapted from Hill et al.,⁵⁷ copyright American Chemical Society.

is known that pyridine does not demonstrate Brønsted acid sites on alumina due to weak strength,⁵⁹ while being a much stronger base, NH_3 does.⁶⁰

Carbon dioxide (CO_2) IR spectroscopy

HAp naturally exhibits surface carbonates due to CO_2 adsorption from the environment, and bulk carbonates from dissolved CO_2 in alkaline water, substituting PO_4^{3-} ions during HAp synthesis.^{33,38} Therefore, accurately interpreting IR spectra while using CO_2 as a probe for surface basic sites in HAp is quite a complex task—one without a clear advantage over other more revealing probe molecules. Studies employing CO_2 probe IR spectroscopy for surface characterization of HAp samples have demonstrated that, upon CO_2 adsorption, an increase in the pre-existing carbonates and hydroxyls in the HAp sample was observed.³⁸ To date, the exact type and structure of the adsorbed species is not fully understood, as the position and intensity of various IR peaks observed is very sensitive to the temperature of the experiment and the nature of the HAp sample. For example, as summarized in Table 1, three representative reports assign various IR peaks observed during CO_2 IR spectroscopy to different kinds of carbonate and bicarbonate structures in contradiction with each other. It suffices to note here that, despite disagreement in the exact band assignments—which in itself is not trivial, the formation of hydroxycarbonates/bicarbonates and other various forms of bulk and surface carbonate species upon CO_2 adsorption is unanimously accepted among the HAp catalysis community.^{25,38,57}

Acetylene (C_2H_2) IR spectroscopy

Another effective probe to study the nature of surface sites in HAp is acetylene (C_2H_2). C_2H_2 can adsorb non-dissociatively onto the surface sites in various configurations: (1) a π complex parallel to the surface with a Brønsted or Lewis acid site via the interaction of the $\text{C}\equiv\text{C}$ bond with the surface sites,^{38,57} (2) a σ complex

Table 1. Literature summary of IR peak assignments for CO₂ adsorption IR studies on HAp catalysts, highlighting the disagreement on the exact type and nature of adsorbates formed

Wavenumber (cm ⁻¹)	Assignment	Reference
1,701	bicarbonate	Hill et al. ⁵⁷
1,624	bidentate bicarbonate	Hill et al. ⁵⁷
1,597	bidentate carbonate	Hill et al. ⁵⁷
1,360	bidentate carbonate	Hill et al. ⁵⁷
1,545–1,456	bulk type B carbonate	Diallo-Garcia et al. ³⁸
1,501–1,444–1,414	bulk type A carbonate	Diallo-Garcia et al. ³⁸
1,420–1,409	surface type A carbonate	Diallo-Garcia et al. ³⁸
1,485–1,385	surface (PO ₄) _s -carbonate	Diallo-Garcia et al. ³⁸
1,370–1,345	surface (PO ₄) _s -carbonate	Diallo-Garcia et al. ³⁸
1,758–1,704–1,673–1,664–1,610–1,590	$\nu(\text{OCO})_{\text{as}}$ bicarbonate	Diallo-Garcia et al. ³⁸
1,398 or 1,390	$\nu(\text{OCO})_{\text{s}}$ bicarbonate	Diallo-Garcia et al. ³⁸
1,180–1,240	$\delta(\text{COH})$ bicarbonate	Diallo-Garcia et al. ³⁸
1,482, 1,345–1,370	monodentate carbonate on CaO-PO _x	Ho et al. ²⁵
1,442–1,400	monodentate carbonate on CaO	Ho et al. ²⁵
1,710–1,590	monodentate bicarbonate	Ho et al. ²⁵

(PO₄)_s, chemisorbed carbonates on PO_x surface sites

perpendicular to the surface with a Brønsted basic site via the interaction of one hydrogen,³⁸ (3) a π - σ complex parallel to the surface with an adjacent acid-base pair.³⁸ C₂H₂ can also adsorb dissociatively onto strong basic sites, which would result in the formation of an OH group.³⁸

The lack of perturbation in the P-O vibrations upon C₂H₂ adsorption was used to conclude that the adsorption occurred at the basic OH groups and not the basic, unprotonated PO₄³⁻ sites on the surface.³⁸ Results also showed that IR peaks corresponding to the P-OH groups were perturbed, suggesting that P-OH were serving as the Brønsted acid sites.³⁸ No evidence for dissociative adsorption of C₂H₂ on strongly basic surface sites was observed. The three unique surface sites and the three types of non-dissociative adsorptions demonstrated for acetylene on HAp are summarized below and depicted in Figure 6:

1. The π complex formation on isolated, mild Brønsted acidic sites (P-OH) led to only one C-H vibration of the acetylene molecule, with neither of the two acetylene protons being directly involved in the interaction. Therefore, the C-H vibration was only slightly red-shifted compared with the gas-phase IR peak at 3,237 cm⁻¹.³⁸ These sites are indicated in red in Figure 6.
2. The π - σ complex formation over a Brønsted acid-base pair on the HAp surface led to two unique C-H IR peaks. The two IR peaks at 3,214 and 3,099 cm⁻¹ were found to be affected similarly during the desorption step and therefore assigned to a C₂H₂ adsorbed non-dissociatively on an acid-base pair in a parallel configuration. Also note here that both C-H bands are red-shifted in comparison with gas-phase C₂H₂, indicating elongation.³⁸ These sites are indicated in green in Figure 6.
3. The σ complex formation on isolated, medium-strength Brønsted basic sites (OH) led to two distinct C-H bands at 3,178 and 3,281 cm⁻¹. In this case, one C-H bond is elongated due to interaction with a basic surface OH site, while the other hydrogen of C₂H₂, which is at the other end and dangling, is shortened compared with gas-phase C₂H₂, indicating perpendicular adsorption of C₂H₂ onto a surface hydroxyl.³⁸ These species are indicated in blue in Figure 6.

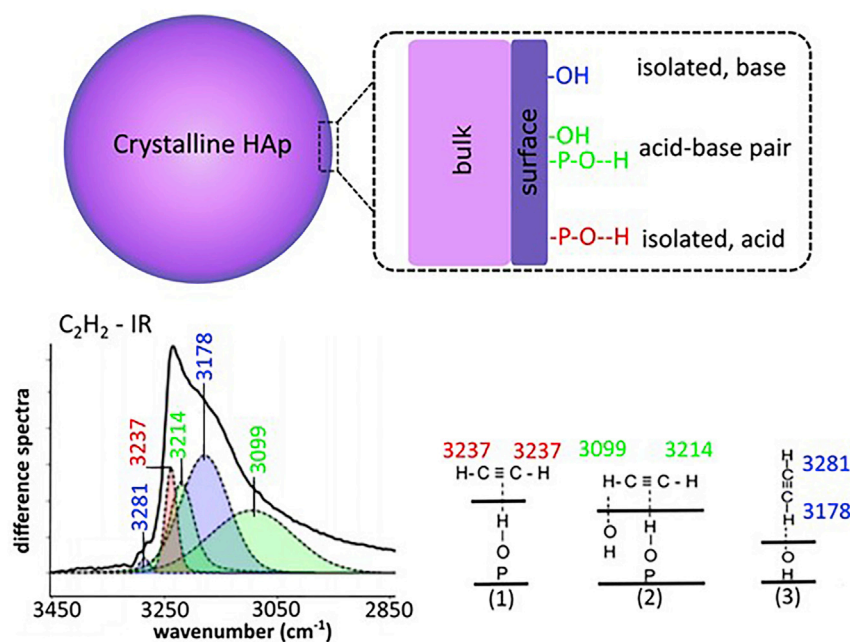


Figure 6. Acetylene adsorption IR spectroscopy of HAp catalysts.

Surface acidic and basic sites probed with C_2H_2 adsorption suggest the presence of Brønsted acid sites (P-OH) and Brønsted base sites ($-OH$) on the surface.

Data adapted from Diallo-Garcia et al.,³⁸ copyright American Chemical Society.

Summarily, C_2H_2 adsorbed non-dissociatively onto the HAp surface and predominantly interacted with the surface OH groups. These weakly basic OH groups (presumably Ca-OH) were involved in two non-dissociative adsorption modes. As the PO_4^{3-} IR peaks were not perturbed by C_2H_2 adsorption, it was concluded that the basic O^{2-} of PO_4^{3-} is not involved in C_2H_2 adsorption or might not be present on the surface. The absence of P-O perturbation upon C_2H_2 adsorption also corroborates findings from the MAS-NMR study, which suggested that the HAp surface, even at elevated temperature, is largely populated with $H_xP_xO_4^{(3-x)}$ and not with PO_4^{3-} .³⁶ Note, that when the OH groups are associated with P, as in P-OH, they become mild-strength Brønsted acid sites. Since these mildly acidic P-OH sites were found to be involved in a non-dissociative C_2H_2 adsorption mode, their role in catalytic reactions becomes relevant. Most importantly, the presence of acid-base pairs on the HAp surface that led to π - σ complex formation upon C_2H_2 adsorption is a unique site that requires further attention and evaluation, given their critical relevance to acid-base (bifunctional) catalytic applications. Avenues requiring further work include (1) quantifying the density of such acid-base pairs on HAp surfaces with relevance to Ca/P ratio and various synthesis techniques, (2) understanding and tuning the strength of isolated acid or base sites versus the acid-base pairs, and (3) unraveling the role of acid-base pairs and isolated sites in catalytic reactions via *operando* and modulation-excitation characterization techniques.

RATIONALIZING STRUCTURE-REACTIVITY RELATIONSHIPS IN HAP-CATALYZED C=C COUPLING

C-C coupling of alcohols constitutes a large volume of reports on HAp catalysis, and the following discussion will focus on the structure-function relationships of HAp catalysts during C-C coupling reactions. Rigorous evidence (spectroscopy; transient kinetics; steady-state kinetics) in the literature point toward ethanol to butanol

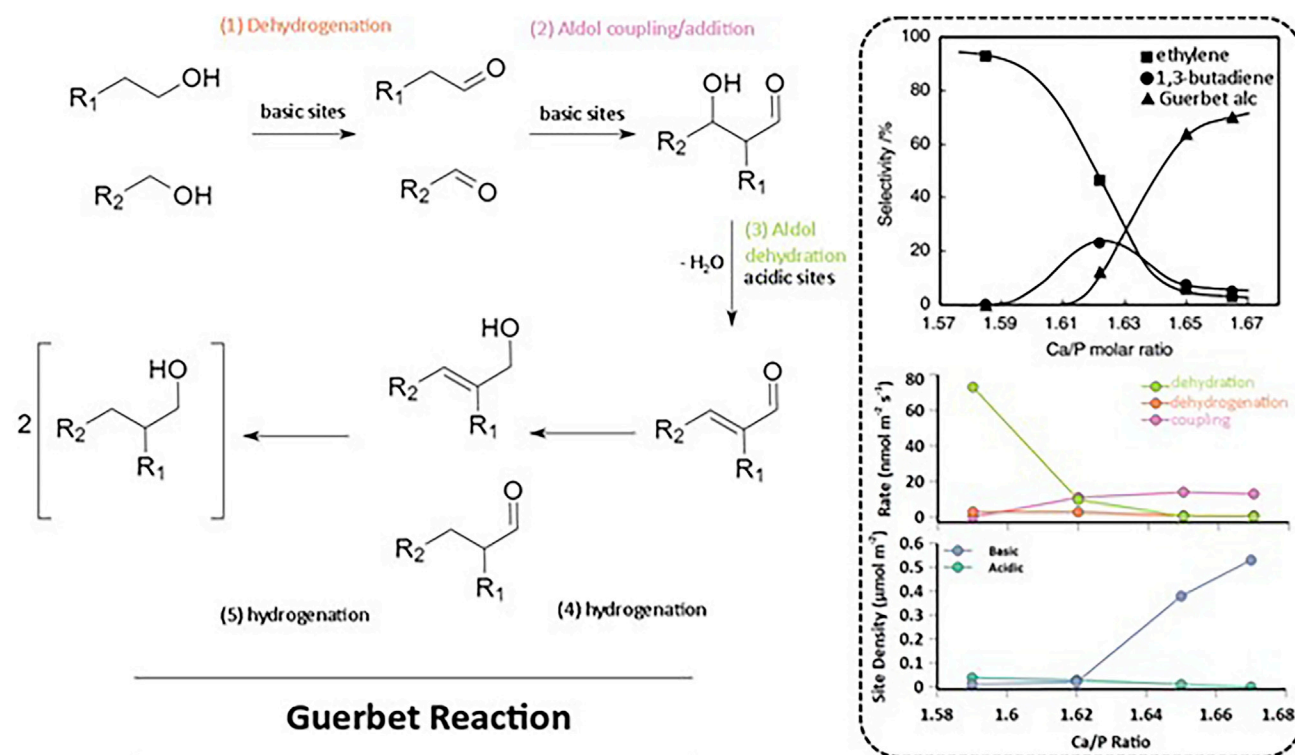


Figure 7. The Guerbet reaction of primary alcohols

(Left) Guerbet reaction mechanism for primary alcohols. (Right) Panels showing the dependence of reaction rates and product selectivities in Guerbet coupling of ethanol on the acidic and basic nature of surface sites in HAP. As the Ca/P molar ratio increases, the density of basic sites also increases, resulting in a systematic decrease in the acid-catalyzed dehydration step rate. Likewise, as the Ca/P increases, the surface basic site density also increases and, as a result, the selectivity to ethylene by-product (from acid-catalyzed dehydration of ethanol) decreases while the selectivity toward Guerbet-coupled alcohols (desired) increases, indicating the importance of basic surface site density for the Guerbet mechanism. Finally, selectivity toward 1,3-butadiene by-product formation from dehydration of crotonaldehyde intermediate goes through a maximum value because, at Ca/P of ~ 1.62 , an optimum balance is reached between the acidic and basic surface site densities, which was hypothesized to promote a secondary reaction pathway “Lebedev reaction” where 1,3-butadiene is the main product. Information and figure are adapted from Tsuchida et al.¹¹ and Kozłowski and Davis.¹⁷

reaction following the Guerbet mechanism.^{17–19,22,24,25,28,61} However, some evidence is present in the literature from 2014–2015 for the so-called ‘direct’ mechanism of ethanol coupling as well.^{20,62} Given the general consensus on the Guerbet mechanism, we will discuss the surface chemistry of HAP with regard to Guerbet mechanism only. Utilizing HAP for *n*-C₄H₉OH synthesis via the Guerbet reaction of C₂H₅OH circumvents the previously employed industrial Oxo process.⁶³ The Oxo process consists of two successive reactions: the hydroformylation of propylene with syngas (carbon monoxide and hydrogen) from crude oil over cobalt or rhodium catalysts at high pressure to synthesize aldehyde, and the hydrogenation of this aldehyde over a nickel catalyst to yield *n*-C₄H₉OH.^{3,63} The Oxo process is extremely problematic from both economical and environmental standpoints, as it requires a high-pressure reaction of propylene with syngas—a steam reforming product. A pioneering study from 2006,⁶³ reported Hap-catalyzed coupling of C₂H₅OH into *n*-C₄H₉OH with a 76% selectivity at atmospheric pressure, which initiated the vibrant field of catalytic upgrading of bio-feedstock relevant alcohols (especially C₂H₅OH) into high-value fuels and chemicals.

The general Guerbet reaction mechanism, depicted in Figure 7, encompasses the most widely accepted five reaction steps that were verified by kinetic isotope switch

experiments and spectroscopy. The first step of the catalytic Guerbet reaction involves oxidation (dehydrogenation) of the primary alcohol over the basic sites to form corresponding surface-bound aldehyde species, which undergo aldol condensation over basic surface sites to yield the surface-bound condensation product. This condensation product then dehydrates to unsaturated aldehyde surface-bound species over the acidic surface sites of the catalyst. Once the unsaturated aldehyde species are formed, they undergo hydrogenation either on the surface or in the gas phase to produce the final product. To highlight the importance of acid-base sites for the corresponding steps involved in the Guerbet reaction, the right panel in [Figure 7](#) shows the variation in Ca/P ratio, which likely changes the surface acid-base site balance and consequently the selectivity of the HAp-based catalysts by controlling the rate of dehydration, dehydrogenation, and aldol-coupling steps.²¹ Contrary to previous assumptions, a study has also shown that the Ca/P ratio does not always correlate directly with the acidity or basicity of the HAp catalysts. Specifically, the Ca/P = 1.65 sample was shown to be more basic (and hence more active for the oxidation of a probe molecule 2-methyl-3-butyn-2-ol) than samples with Ca/P = 1.67 and 1.77.¹⁰ The Ca/P ratio was confirmed using inductively coupled plasma atomic emission spectroscopy, and the authors hypothesized that, besides the Ca/P ratio, the degree of carbonation and the amount of OH defects in HAp also contribute toward the final acidic and basic character of the surface sites.¹⁰ Given the dependence of reaction rates for each step on surface acid-base sites, the importance of state-of-the-art understanding regarding the composition of a surface, the nature of those acid and base sites provided in the previous sections becomes clear.

C₂H₅OH interaction with the surface sites; steps 1–3

The HAp surface is populated by weak acidic and moderate strength basic sites, which also exist as acid-base pairs. C₂H₅OH adsorption on HAp surface sites constitutes the first elementary step in Guerbet-type reactions. An important distinction is regarding the identity of adsorption sites and the mode of adsorption. C₂H₅OH can adsorb on the surface in two ways, e.g., (1) molecularly as intact C₂H₅OH* and (2) dissociatively as C₂H₅O* and H*.^{64–66} For molecularly adsorbed species, the final structure of the adsorbate resembles that of the free C₂H₅OH molecule. On the other hand, the dissociatively adsorbed species lead to surface bound species, such as C₂H₅O*, and indicate more favorable (exothermic) binding to the surface sites.

Upon C₂H₅OH adsorption at room temperature on HAp, three distinct bands were observed in the C-H region: 2,975 ν_{as}(CH₃), 2,930 ν_{as}(CH₂), and 2,903 cm^{−1} ν_{as}(CH₃), corresponding to the ethoxy species formed from dissociatively adsorbed C₂H₅OH.^{61,67} Given the decrease in intensity of ~3,570 and ~3,670 cm^{−1} peaks upon C₂H₅OH adsorption, it was concluded that adsorption occurred on both Lewis basic OH[−] and Brønsted acidic P-OH sites.⁶⁷ Elsewhere in the literature, adsorption of propanal (C₃H₆O) on surface Lewis basic (OH[−]) and Brønsted acid (P-OH) sites on HAp also supports the involvement of these sites in adsorption.²⁹ However, the literature does not discuss the effect of C₂H₅OH adsorption on the ~3,500 cm^{−1} band that is observed but not assigned across various reports, as highlighted in a previous section of this review. Moreover, while a decrease in IR peak intensities suggests interaction between adsorption sites and the adsorbate, TPD-IR studies are absent that can shed light if any new O-H sites are generated *in situ* as the adsorbed C₂H₅OH desorbs/reacts with increasing temperature. Two new peaks were observed upon C₂H₅OH adsorption at 1,385 and 1,495 cm^{−1}, which were attributed to adsorbed ethoxy (C₂H₅O*) and acetate (CH₃COO*) species on the HAp surface, respectively.⁶⁷ A weak shoulder at 1,660 cm^{−1} further corroborated the presence of C-O vibrations from surface acetate species. As the temperature increased, IR bands

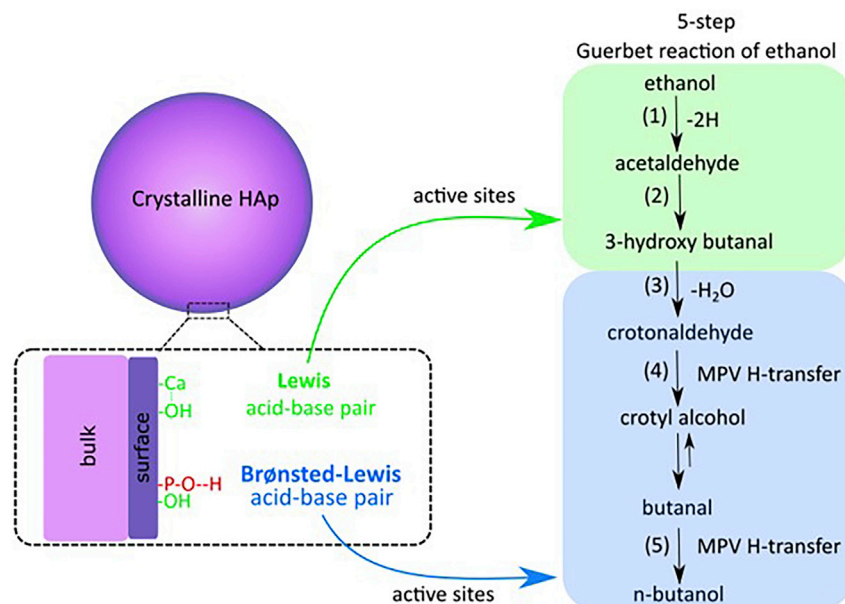


Figure 8. Summary of literature proposed active sites for various steps in the Guerbet reaction of C_2H_5OH to $n-C_4H_9OH$ over HAp catalysts

corresponding to ethoxy species weakened significantly, and completely disappeared by 573 K, indicating the moderate strength of adsorption sites.⁶¹ Surprisingly, no vibration in the carbonyl region ($1,700\text{--}1,800\text{ cm}^{-1}$) was reported upon C_2H_5OH adsorption on HAp in any IR spectroscopy study¹⁹ until recently, where a modulation-excitation approach demonstrated an IR peak at $1,758\text{ cm}^{-1}$, confirming the formation of surface-bound acetaldehyde (CH_3CHO).¹⁹ We caution the reader that a majority of studies reporting *in situ* IR spectroscopy of C_2H_5OH -adsorption on HAp do so at low temperatures where condensed phase ethanol may be present, and do not employ the informative TPD approach. Conducting IR studies with flowing C_2H_5OH throughout the duration of the study is also problematic, as water and condensed C_2H_5OH can be present on the surface at low temperatures ($\sim 373\text{ K}$), obscuring the weaker intensity bands and their respective assignments from the reaction intermediates. To the best of our knowledge, a systematic TPD-IR study has also not been conducted on the strength and density of C_2H_5OH binding sites in HAp as a function of Ca/P ratio to unravel the effect of surface acid-base balance on interaction with probe or reactant molecules. Therefore, TPD-IR studies are necessary to further understand HAp catalysts under working conditions.

It is generally accepted that surface-bound ethoxy is dehydrogenated/oxidized to acetaldehyde, which self-aldol couples over basic sites.^{19,21} The coupling product then likely dehydrates over Brønsted acidic sites to yield crotonaldehyde, completing the aldol condensation pathway.^{19,21} Although there was uncertainty regarding the active sites for the Guerbet reaction over HAp, as summarized in Figure 8 based on recent modulation-excitation (M-E)-DRIFTS results, it is likely that the Lewis acid-base pair (Ca^{2+} and OH^-) serves as the active sites for steps 1–2 of the HAp-catalyzed Guerbet reaction to produce $n-C_4H_9OH$ from C_2H_5OH .¹⁹ Elsewhere, poisoning experiments with two acidic probe molecules of different acidic strengths, i.e., CO_2 and propionic acid revealed that acetaldehyde and butanol formation rates decreased to varying extents with the introduction of each acidic probe, demonstrating that the basic sites for the various reaction steps, specifically step 1 versus

steps 2–5, are not identical.²⁵ Based on complementary *in situ* CO₂ IR study results, it was further suggested that ethanol dehydrogenation to acetaldehyde was likely catalyzed by the Ca–O surface sites where the CO₂ probe adsorbed weakly, leading to a lack of significant inhibitory effect. On the other hand, all subsequent steps to yield the butanol product were proposed to be over Ca–O–PO_x interfacial sites, where acidic probes, such as CO₂, adsorbed strongly and exhibited a severe inhibitory effect.²⁵

Critical insights inferred from kinetics studies also corroborate the spectroscopic insights summarized above. For example, the steady-state rate of aldol condensation of acetaldehyde to crotonaldehyde (steps 2–3) over HAp showed an approximately first-order dependence on acetaldehyde partial pressure, and an extremely low activation barrier as the reaction was found to be temperature independent.²⁸ Moreover, isotope switch experiments using fully deuterated acetaldehyde did not exhibit a kinetic isotope effect in the first-order rate constant in comparison with the H-form acetaldehyde, suggesting that C–H activation was not kinetically relevant and likely not involved in the rate-determining step.²⁸ These results signified that the C–H activation cannot be the kinetically relevant reaction step and hence enolate formation (i.e., α -H abstraction from the surface-bound aldehyde) was not the slow step. Other aldol condensation steps do not involve C–H activation and thus can be ruled out as rate determining.²⁸ It was suggested that the rate-determining steps likely were the desorption of products, including crotonaldehyde and water.²⁸ A recent in-depth kinetic study confirmed that competitive adsorption of water inhibits ethanol coupling over HAp; however, this inhibition can be fully reversed by removing water from the feed.²⁴ It should be noted that the C–H activation is not kinetically relevant if acetaldehyde aldol condensation to crotonaldehyde is being studied exclusively. However, if the full Guerbet reaction of ethanol to *n*-butanol over HAp is considered where acetaldehyde intermediate is formed from ethanol dehydrogenation,²⁵ followed by acetaldehyde aldol condensation to crotonaldehyde, and finally hydrogenation of crotonaldehyde to *n*-butanol, the C–H activation step during aldol coupling does become kinetically relevant.^{24,25,61} As the Guerbet reaction involves hydrogenation of surface-bound aldol condensation intermediates, the product desorption barrier likely decreases due to hydrogenation, making desorption facile.

Hydrogenation during the Guerbet reaction of C₂H₅OH; steps 4–5

The hydrogenation steps (4–5) in the HAp-catalyzed Guerbet reaction were not well understood until recently. Two different hydrogenation pathways can be possible: (1) surface-mediated hydrogenation of the C=C bond of unsaturated alcohol (crotyl alcohol), where the surface hydrogen comes from C₂H₅OH dehydrogenation in the first step,^{19,68,69} and (2) direct hydrogenation of C=O in butanal (from isomerization + tautomerization of crotyl alcohol) by C₂H₅OH via the Meerwein-Ponndorf-Verley (MPV) reaction.^{18,19,27,68} On transition metal catalysts, such as copper, gas-phase molecular hydrogen rapidly exchanges,¹⁷ so the hydrogenation and dehydrogenation mechanisms on metal-containing catalysts are usually surface mediated. However, hydrogenation/dehydrogenation mechanisms on metal oxides and metal phosphates are not well understood and expected to be different than their metal counterparts.¹⁷ Recent literature has provided more evidence of MPV mechanism prevailing over HAp as D₂ and H₂ isotopic exchange did not occur over HAp, and, upon D₂ introduction, deuterated products were not observed, indicating that hydrogen for the hydrogenation reaction steps was sourced from the reactant C₂H₅OH molecules.^{18,19} Moreover, all of the hydrogen transfer reactions (i.e., steps 4–5) during Guerbet coupling involve MPV-like

reactions between the sacrificial H-donor alcohol and the C=O intermediates.¹⁸ No evidence for C=C hydrogenation was observed, which suggests hydrogenation via MPV-hydrogen transfer steps likely undergo a double bond shift to form an enol, which is tautomerized to a C=O before hydrogenation.¹⁸ In agreement with these findings, recent *operando* M-E-DRIFTS also provide spectroscopic evidence for hydrogenation of C=O in butanal intermediate.¹⁹ The M-E-DRIFTS results point toward a hydrogen transfer between reactant C₂H₅OH and intermediate butanal to form *n*-C₄H₉OH product over P-OH – OH[–] acid-base pair on the HAp surface.¹⁹ The relevance of the MPV hydrogenation pathway to surface P-OH sites was also corroborated by the fact that, when Brønsted acidic P-OH sites are selectively poisoned, the *n*-C₄H₉OH product from hydrogenation of butanal intermediate is not observed.³²

Summarily, based on the literature analyzed within this review, the Lewis acid-base pair (Ca²⁺–OH[–]) is proposed to be the main active site for steps 1–2 of the Guerbet reaction, which includes dehydrogenation and aldol coupling. On the other hand, the Brønsted-Lewis acid-base pair (P-OH–OH[–]) is proposed as the main site for steps 3–5, including dehydration of the aldol coupling product to complete aldol condensation, and subsequent hydrogenation of unsaturated aldol products (C=O) via the MPV route. Note that this distinctive Brønsted-Lewis acid-base pair was first identified as a surface site unique to HAp via acetylene IR spectroscopy.³⁸ Noting the linear length of the acetylene molecule,^{70,71} it is suggested that this acid-base pair is ca. 166 pm (1.6 Å) apart. The proposed active sites are summarized in Figure 8.

OUTLOOK

Overall, the HAp catalysis literature seems to suggest that the Lewis acid-base pair (Ca²⁺–OH[–]) is the main active site for steps 1–2 of the Guerbet reaction, which includes dehydrogenation and aldol coupling, while Brønsted-Lewis acid-base pair (P-OH–OH[–]) seems to be the main active site for steps 3–5, including dehydration of the aldol coupling product to complete aldol condensation, and subsequent hydrogenation of unsaturated aldol products via the MPV route. However, a few critical pieces of the surface mechanism remain unclear. Previously, it has been proposed that the primary handle on HAp acid and basic properties was the Ca/P molar ratio, adjusted by varying the precursor concentrations during synthesis. However, recent studies employing advanced characterization of HAp samples demonstrate that the surface chemistry is much more complex.^{17–19,21} By using test reactions in conjunction with detailed surface characterization, it has been shown that, even at a stoichiometric Ca/P ratio of 1.67, the degree of carbonation during synthesis and the population of OH and related defects strongly affect the bifunctional (acid-base) nature of the final HAp catalyst. Another reason for the discrepancy between the hypothesized activity of various acid-base sites toward each reaction step in C–C coupling and the observed rates can be the use of unsuitable probe molecules utilized in spectroscopic studies. Experts in the field acknowledge that more reactant-like probe molecules are needed to be used to effectively probe the nature of surface sites in HAp and generate reaction-relevant mechanistic insights.¹⁷

It is proposed that further advancement of the fundamental structure-reactivity relationships of HAp-catalyzed C–C coupling reactions that can address the information gap and guide the rational design of improved catalysts will require the following:

1. *In situ* and *operando* temperature-programmed spectroscopic studies, especially IR and Raman spectroscopy, and NAP-XPS of HAp-catalyzed C–C coupling reactions to elucidate the structural and compositional dynamics of various surface species being generated or consumed at/near reaction conditions. The most advanced studies will also involve modulation-excitation spectroscopy, as recently demonstrated.¹⁹ During modulation-excitation, when a catalytic system is perturbed via modulation of a parameter (e.g., reactant partial pressure) under quasi-steady-state conditions, reaction intermediates will oscillate with the same frequency as the perturbation. After multiple data are averaged during modulation-excitation, the signal from active surface species will be enhanced while the spectator surface species will not respond to the stimulation, providing researchers an unprecedented tool to distinguish spectator surface species.^{19,72} Finally, ISS (also called LEIS) and GIXD/SXRD^{73–75} studies need to be conducted on a series of well-defined HAp catalysts to ascertain the true surface composition of catalysts (i.e., surface termination/enrichment) and its effect on the C₂H₅OH coupling activity and selectivity of those catalysts.
2. It is known that moderately basic and weakly acidic sites are required for an effective Guerbet reaction catalyst, which HAp surface is known to possess. Future studies need to characterize and test model catalysts to shed light on the proximity of the acid-base pair, and what makes those sites unique to HAp. It is yet to be ascertained whether a monolayer catalyst with H_xPO_y and CaO_x surface sites supported on a high surface area support can replace the traditionally used low surface area HAp catalysts. Moreover, the role of surface P=O sites in HAp toward the Guerbet reaction has not been studied in detail. For example, recently spectroscopic evidence has emerged for the involvement of such P=O surface sites participating in surface-mediated H transfer reaction, where ethanol serves as the H-donor.²³ Therefore, the role of P=O surface sites and their potential involvement in the surface-mediated H transfer reaction (i.e., steps 4–5 of the Guerbet reaction) needs to be studied further.
3. Since the structure and nature of PO_x and H_xPO_y in the topmost atomic layer of HAp is not well known (isolated PO_x versus dimeric versus oligomeric; isolated H_xPO_y versus dimeric versus oligomer), model catalysts need to be studied with phosphates supported on high surface area supports as a function of Ca promotion and P loading to elucidate the nature and structure of surface H_xP_yO_z. *In situ* and *operando* Raman spectroscopy can be utilized to systematically distinguish between various types of surface H_xP_yO_z sites. Reactivity for such model catalysts can be explicitly studied via transient methods, including temperature-programmed surface reaction.⁷⁶
4. Elsewhere in the literature, it is known that HAp possesses OH[−] ion channels ~3 Å in diameter, which enable the mobility of OH ions in the bulk.⁸ Likewise, another study has also reported sinusoidal H⁺ channels within HAp, with proton mobility demonstrated at 298–923 K.⁷⁷ To date, a profound mechanistic role of these OH[−] and H⁺ channels in HAp-catalyzed reactions (especially ethanol coupling) has not been elucidated. While most HAp catalysis literature does not allude to these channels otherwise discussed in bio-related applications of HAp, some recent reports have started to appreciate and investigate their role toward C–H activation over HAp-based catalysts.^{32,78} Dedicated computational and experimental studies are required to fully ascertain the potential role of these channels unique to HAp toward catalytic applications. Curious readers are directed to mechanistic studies from broader literature regarding the unique ion channels and how they affect HAp's properties.^{79–83}

5. Finally, the potential involvement of acidic $\text{H}_x\text{CO}_3^{(2-x)}$ surface sites needs to be studied with respect to various reaction steps in the Guerbet mechanism using *in situ* and *operando* spectroscopic studies including chemical probe IR spectroscopy. For instance, the H-transfer capability of carbonate surface sites has been demonstrated: it was observed that in the absence of water, carbonic acid (H_2CO_3) surface intermediate formed upon adsorption of various H-donor probe molecules (CH_3COOH , HNO_3 , HCOOH) onto CaCO_3 where surface $\text{H}_x\text{CO}_3^{(2-x)}$ sites were present and transferred the hydrogen from the H-donor molecules.⁸⁴ Therefore, a systematic study is required to elucidate how the surface chemistry of HAp catalysts is influenced by surface $\text{H}_x\text{CO}_3^{(2-x)}$ sites by using model catalytic systems and suitable probe molecules.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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